The Annual Report on Postnatal Diagnostic Testing in Victoria, 2022

Reproductive Epidemiology group

Genomic Medicine theme

Murdoch Children's Research institute

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This report is produced by the **Reproductive Epidemiology group** in the Genomic Medicine theme at the MCRI. For more information about us, go to our page at

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Background

The most common cause of spontaneous miscarriage is aneuploidy. When women experience a pregnancy loss, postnatal chromosome analysis may be offered, particularly in the setting of recurrent miscarriage. Molecular karyotyping with chromosomal microarrays is preferred over G-banded karyotype for postnatal samples. As there is no requirement for cell culture with this technique, failure rates are low. This report on postnatal chromosome testing complements the Victorian Prenatal Diagnosis Report, providing results for women resident in Victoria, Australia. It includes samples taken in 2022 from placenta, umbilical cord, fetal tissue and "products of conception" (POC) but no paediatric samples.

We acknowledge our collaborators – the Victorian Clinical Genetics Service and Monash Pathology – who contributed the data contained in this report.

Definitions

Major chromosome conditions: autosomal trisomies, autosomal monosomies, polyploidy, sex chromosome aneuploidies, pathogenic copy number variants (CNVs), unbalanced rearrangements, gestational trophoblastic disease, uniparental disomy (UPD) involving an imprinted chromosome, and high-level mosaicism.

Minor chromosome conditions: genomic CNVs of uncertain or unknown significance, long continuous stretches of homozygosity (LCSH), confined placental mosaicism (CPM), and balanced rearrangements.

Diagnostic yield: the percentage of women with a major fetal chromosome condition confirmed on diagnostic testing as a proportion of total tests.

Positive non-invasive prenatal testing (NIPT) result: 'increased chance', 'high risk', 'aneuploidy detected' or other result indicating an increased probability of a chromosome condition in the pregnancy.

Classification of genomic copy number variants (CNVs): CNVs were classified as *pathogenic, likely pathogenic, uncertain, or unknown significance, likely benign, or benign* according to the clinical laboratory interpretation, which is guided by the American College of Medical Genetics standards and guidelines for interpretation and reporting of copy number variants.[1, 2]

Variant of uncertain or unknown significance (VUS): CNV with uncertain, or unknown clinical significance as classified by the reporting laboratory

Summary statistics

In 2022, 1155 postnatal samples were referred for diagnostic testing. Of these, 3.5% (40/1155) were found through record linkage to also have had a prenatal diagnostic test in the same pregnancy. All samples were evaluated by chromosomal microarray or both chromosomal microarray and karyotyping.

Specimen types

Postnatal specimens included 562 "POC" samples (unspecified), 307 placental biopsy/cyst/villus samples, and 286 fetal tissue samples (**Table 1**). The pregnancy outcome of the postnatal samples was inconsistently recorded in the clinical referrals for testing. A livebirth was presumed in 13 (1.1%) based on the indication for testing, e.g., a placental biopsy to investigate fetoplacental mosaicism, when a high chance NIPT result was followed by a 'normal' result on amniocentesis (n= 10).

Table 1. Specimen types

Specimen types	n (%)
'POC' (unspecified)	562 (48.7)
Placenta (biopsy, cyst, villus)	307 (26.6)
Fetal (fetal tissue, rib/cartilage, skin, spleen)	286 (24.8)
Total	**1155 (100.0)**

Gestational age

Gestational age at delivery was available for 518 (44.8%) of specimens. (**Table 2**).

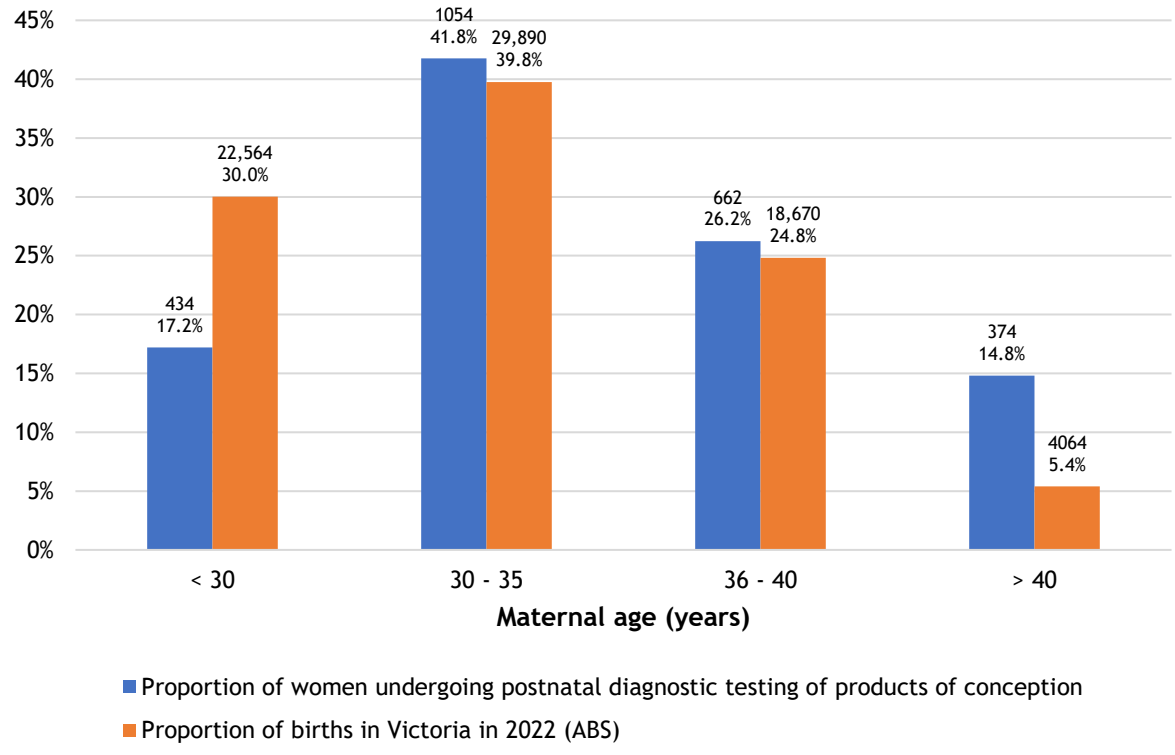
Table 2. Gestational age

Gestational age (weeks)	n (%)
<14	254 (22.0)
14 - 23	207 (17.9)
≥ 24	57 (4.9)
Missing data	637 (55.2)
Total	**1155 (100.0)**

Maternal age

Maternal age at the time of diagnostic testing is shown below. The most common maternal age group was 30-35 years (**Figure 1**). This age distribution is compared to the proportion of mothers who gave birth (at ≥20 weeks) in Victoria in 2022 (Australian Bureau of Statistics; https://www.abs.gov.au).

Figure 1. Maternal age at diagnostic test date and amongst women giving birth



Indications for postnatal diagnostic testing

Testing indications were recorded according to the written clinical referral. Independent verification of the indications for testing was not performed. More than one indication could be recorded for each sample. Consequently, there were 1406 indications recorded for 1155 postnatal samples.

The most common reason for postnatal diagnostic testing was pregnancy loss at < 20 weeks' gestation (22.6%), followed by fetal loss at an unspecified gestation (22.3%), and fetal abnormality on ultrasound (16.0%) (**Table 3**).

Table 3. Indications for postnatal diagnostic testing

Indication	n (%)
Pregnancy loss at < 20 weeks' gestation[1]	318 (22.6)
Fetal loss, gestation unspecified	313 (22.3)
Fetal abnormality on antenatal ultrasound[2]	225 (16.0)
Previous or 'recurrent' miscarriage[3]	210 (14.9)
Termination of pregnancy	115 (8.2)
High chance NIPT result	85 (6.0)
Stillbirth, fetal death in utero, or preterm prelabour rupture of membranes ≥ 20 weeks	69 (4.9)
High chance first trimester combined or second trimester serum screening result	10 (0.7)
Other[4]	61 (4.3)
Total	**1406 (100.0)**

NIPT, non-invasive prenatal testing

[1]Indications for pregnancy loss < 20 weeks included: 'miscarriage', 'missed abortion', 'preterm premature rupture of membranes', and 'fetal demise'.

[2]Fetal abnormality on antenatal ultrasound included a structural abnormality, isolated increased nuchal translucency , and isolated absent nasal bone.

[3]'Recurrent' miscarriages included all miscarriages described as 'recurrent' by the clinical referrer.

[4]Other included negative ('low chance') NIPT (n=10), suspected confined placental mosaicism (n=15), single gene condition (n=2), history of chromosomal condition (n=16), suspected chorioamnionitis (n=5), twin-twin transfusion syndrome (n=2), and no clinical notes (n=11).

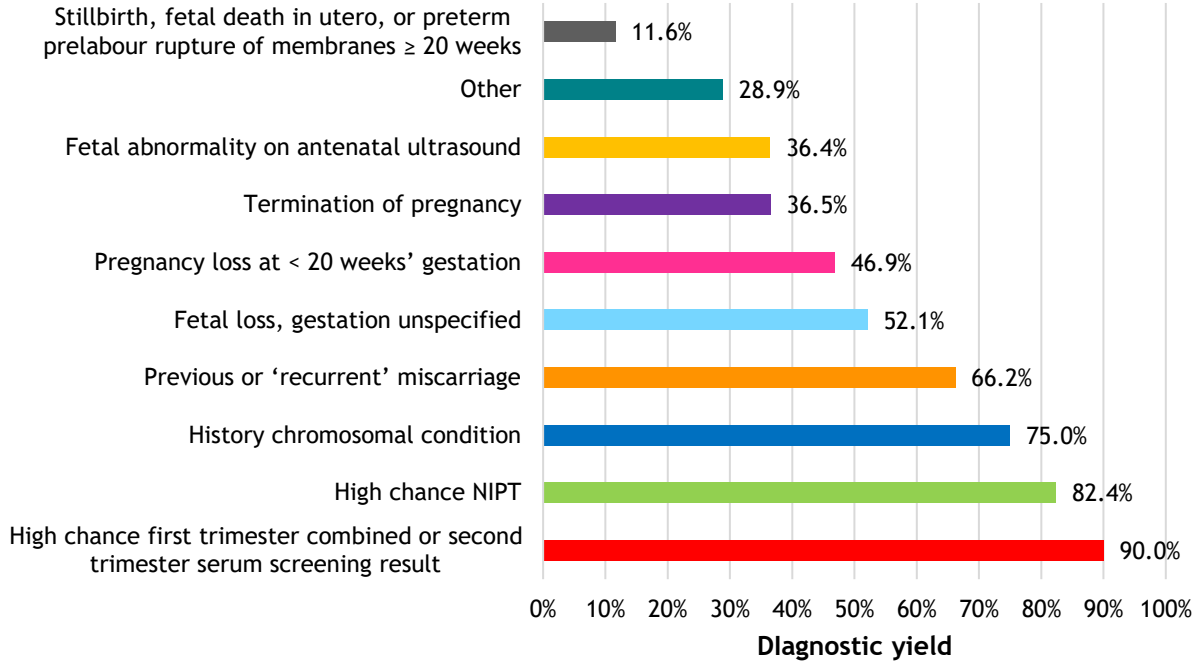
Diagnostic yield

Of the 1155 total postnatal tests, 555 detected a major chromosome condition, resulting in a diagnostic yield of 48.1%.

More than one indication could be recorded for each pregnancy (**Table 3**). Hence, pregnancies may be represented more than once if they have multiple indications for diagnostic testing.

Diagnostic yield was highest for women undergoing testing with a positive ('high chance') first trimester combined screening or second trimester serum screening result (90.0%, 9/10), a positive NIPT result (82.4%, 70/85), a history of a chromosomal condition (75.0%, 12/16), and a previous or 'recurrent' miscarriage (66.2%, 139/210) (**Figure 2**).

Figure 2. Diagnostic yield by indication for testing



NIPT, non-invasive prenatal testing

Indications for pregnancy loss < 20 weeks included: 'miscarriage', 'missed abortion', 'preterm premature rupture of membranes', and 'fetal demise'.

Fetal abnormality on antenatal ultrasound included a structural abnormality, isolated increased nuchal translucency , and isolated absent nasal bone.

'Recurrent' miscarriages included all miscarriages described as 'recurrent' by the clinical referrer.

Other included negative ('low chance') NIPT, suspected confined placental mosaicism, single gene condition, history of chromosomal condition, suspected chorioamnionitis, twin-twin transfusion syndrome, and no clinical notes.

Chromosome results

The most common autosomal trisomies were Trisomy 16, Trisomy 21, and Trisomy 22 (**Table 4**). Turner's syndrome (45, X) was the most frequent sex chromosomal aneuploidy.

Compared to 2020, in 2022 there was an increase in the number of pathogenic CNVs diagnosed. This increase is shown in **Table 4**. In 2022, the most common pathogenic CNV was 22q11.2 deletion (DiGeorge syndrome) (n=4).

Chromosome results by indication for testing

Chromosome results differed by indication for testing. The chromosome results by indications for testing are shown in **Table 5**.

A common autosomal trisomy (trisomy 21, trisomy 18 or trisomy 13) was the most common chromosome result following testing for a positive ('high chance') first trimester screening or second trimester serum screening result (77.8%, 7/9) and a positive NIPT result (54.3%, 38/70).

A rare autosomal trisomy (trisomy other than trisomy 21, 18 or 13) was the most common chromosome result following testing for a previous or 'recurrent' miscarriage (61.2%, 85/139).

The most common indication for testing among those with a pathogenic CNVs was an ultrasound abnormality. This was recorded in 28.3% (13/46) of pathogenic CNVs in 2022.

Table 4. Chromosome results 2020-2022

Result	2020 n (%)	2021 n (%)	2022 n (%)
Normal/benign CNV	615 (48.6)	658 (52.3)	578 (50.0)
Rare autosomal aneuploidies	**222 (17.5)**	**218 (17.3)**	**209 (18.1)**
Trisomy 16	68 (5.4)	65 (5.2)	61 (5.3)
Trisomy 22	49 (3.9)	43 (3.4)	49 (4.2)
Trisomy 15	41 (3.2)	31 (2.5)	42 (3.6)
Other rare autosomal aneuploidy	64 (5.1)	79 (6.3)	57 (4.9)
Common autosomal aneuploidies	**121 (9.6)**	**111 (8.8)**	**114 (9.9)**
Trisomy 21	61 (4.8)	55 (4.4)	56 (4.8)
Trisomy 13	33 (2.6)	27 (2.1)	23 (2.0)
Trisomy 18	27 (2.1)	29 (2.3)	33 (2.9)
Monosomy 21	0 (0.0)	0 (0.0)	2 (0.2)
Sex chromosomal aneuploidies	**61 (4.8)**	**59 (4.7)**	**57 (4.9)**
Turner syndrome (45,X)	59 (4.7)	56 (4.4)	53 (4.6)
Klinefelter syndrome (47,XXY)	3 (0.2)	2 (0.2)	3 (0.3)
Triple XXX (47,XXX)	0 (0.0)	1 (0.1)	1 (0.1)
Other	0 (0.0)	1 (0.1)	
Polyploidy	**67 (5.3)**	**56 (4.4)**	**59 (5.1)**
Pathogenic CNV	24 (1.9)	21 (1.7)	46 (4.0)
Multiple autosomal or sex chromosomal aneuploidies	56 (4.4)	51 (4.1)	20 (1.7)
CNV of uncertain or unknown clinical significance	30 (2.4)	17 (1.4)	14 (1.2)
Gestational trophoblastic disease	12 (0.9)	19 (1.5)	10 (0.9)
Confined placental mosaicism	2 (0.2)	5 (0.4)	4 (0.3)
Other major chromosome condition	39 (3.1)	38 (3.0)	39 (3.4)
Other minor chromosome condition	16 (1.3)*	6 (0.5)	5 (0.4)
Total	**1265 (100.0)**	**1259 (100.0)**	**1155 (100.0)**

CNV; copy number variant

*14/16 minor chromosome conditions in 2020 were a finding of long-continuous stretch of homozygosity (LCSH)

Table 5. Chromosome results by indication for testing

Indication	Total Indications‡	Normal/ benign	Minor chromosome abnormality	Total major chromosome abnormality	Major chromosome abnormalities						
					Common AA^	RAT	SCA	pCNV	Other*	Multiple AA/SCA	Polyploidy
Positive first trimester screening or second trimester serum screening n (%)	10 (100.0)	1 (10.0)	0 (0.0)	9 (90.0)	7 (77.8)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
Positive NIPT n (%)	85 (100.0)	15 (17.6)	0 (0.0)	70 (82.4)	38 (54.3)	3 (4.3)	18 (25.7)	5 (7.1)	6 (8.6)	0 (0.0)	0 (0.0)
History chromosomal condition n (%)	16 (100.0)	4 (25.0)	0 (0.0)	12 (75.0)	0 (0.0)	5 (41.6)	2 (16.7)	3 (25.0)	0 (0.0)	1 (8.3)	1 (8.3)
Previous or 'recurrent' miscarriage n (%)	210 (100.0)	71 (33.8)	0 (0.0)	139 (66.2)	10 (7.2)	85 (61.2)	8 (5.8)	3 (2.6)	9 (6.5)	9 (6.5)	15 (10.8)
Fetal loss, gestation unspecified n (%)	313 (100.0)	150 (47.9)	3 (0.9)	163 (52.1)	25 (15.3)	70 (42.9)	14 (8.6)	9 (5.5)	12 (7.4)	8 (4.9)	25 (15.3)
Pregnancy loss at <20 weeks' gestation n (%)	319 (100.0)	169 (53.0)	3 (0.9)	149 (46.7)	30 (20.1)	62 (41.6)	21 (14.1)	13 (8.7)	7 (4.7)	3 (2.0)	13 (8.7)

Indication	Total Indications‡	Normal/ benign	Minor chromosome abnormality	Total major chromosome abnormality	Major chromosome abnormalities						
					Common AA^	RAT	SCA	pCNV	Other*	Multiple AA/SCA	Polyploidy
Termination of pregnancy n (%)	115 (100.0)	73 (63.5)	0 (0.0)	42 (33.0)	23 (54.8)	2 (4.8)	4 (9.5)	11 (26.2)	0 (0.0)	0 (0.0)	2 (4.8)
Fetal abnormality on antenatal ultrasound n (%)	225 (100.0)	143 (63.6)	8 (3.6)	82 (36.4)	33 (40.2)	9 (10.9)	10 (12.2)	14 (17.1)	12 (14.6)	0 (0.0)	4 (4.9)
Stillbirth, fetal death in utero, or preterm prelabour rupture of membranes ≥20 weeks n (%)	69 (100.0)	61 (88.4)	0 (0.0)	8 (11.6)	3 (37.5)	0 (0.0)	0 (0.0)	3 (37.5)	2 (25.0)	0 (0.0)	0 (0.0)

‡More than one indication could be recorded for each pregnancy. Hence, pregnancies may be represented more than once if they have multiple indications for diagnostic testing.

^Common autosomal aneuploidy included Trisomy 21, Trisomy 18,b and Trisomy 13.

*Other results included mosaic autosomal or sex chromosomal aneuploidies, mosaic pathogenic CNVs, and unbalanced translocations.

AA, autosomal aneuploidy; GTD, gestational trophoblastic disease; pCNV, pathogenic copy number variant; NIPT, non-invasive prenatal testing, RAT, rare autosomal trisomies; SCA, sex chromosomal aneuploidy; Common autosomal aneuploidy included Trisomy 21, Trisomy 18, and Trisomy 13.

References

1. South ST, Lee C, Lamb AN, Higgins AW, Kearney HM. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. Genet Med. 2013;15(11):901-9.

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.